IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	: 1653	**Customer No. 035811**
Examiner	: Chih Min Kam	
Serial No.	: 09/639,859	Docket No.: IPI-04-1174R
Filed	: August 16, 2000	
Inventor(s)	: Leonard S. Girsh	
Title	: THERAPEUTIC STEM CELL GROWTH	
	: FACTOR COMPOSITION, ANTI-	
	: INFLAMMATORY COMPOSITION	
	: AND USES THEREOF	

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Leonard S. Girsh, M.D., hereby declare as follows:

1. I am the sole inventor of the above-referenced application.

2. I have read and understood the Official Action dated March 5, 2004, in which the Examiner has rejected the pending claims as allegedly lacking enablement.

3. The pending claims are directed to an anabolic medicament for treating damaged tissue. The claimed medicament comprises three components:

(a) at least one mucopolysaccharide compound in an amount which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent;

(b) at least one polar surface active lipid; and

(c) a plurality of amino acids, no more than 10% of which are in the D-form, in a molar ratio which is characteristic in healthy tissue of the type being treated for damage.

4. The Examiner states in the March 5, 2004 Official Action that the present specification does not demonstrate an anabolic composition comprising the three components listed in paragraph 3 above, nor has the present specification shown the effect of such

compositions on damaged tissues. The Examiner indicated in the Official Action that, in the (alleged) absence of a demonstration in the present specification showing the use and effect of the claimed compositions, that I would have to provide experimental evidence that the pending claims are enabled.

5. I have treated a 71-year-old female patient who had suffered from Crohn's disease for more than 3 decades. This patient's symptoms included diarrhea, constipation, severe bouts of abdominal pain and fever, G.I. bleeding, generalized aching, extreme fatigue, nausea, and food and dairy intolerance, and she was being treated with 4 mg of corticosteroid, once daily, with no response. Corticosteroid dosing was then increased to 4 times daily for acute flare ups.

6. I administered to this Crohn's disease patient a medicament according to the present invention, comprising about 10.6 g Neocate infant formula containing L-amino acids and glycine, in the genetic code and molar ratio of human tissue (breast milk and stem cell human tissue); about 50-100 mg lecithin; about 12.5-40 mg phosphatidyl choline; about 225 mg EPA from fish oil; 500 mg flaxseed oil (equivalent of about 275-325 mg linolenic acid); and extracellular matrix components comprising collagen, proteoglycan aggregate complex of cartilage and chondroitin sulfate (shark cartilage 740 mg per capsule, twice daily).

7. For ease of comparison to the elements appearing in claim 1 of the present application, I list below components of the medicament used to treat this Crohn's disease patient in terms of the language used in claim 1.

Medicament for treatment of Crohn's disease patient	**Claim 1**
extracellular matrix components comprising collagen, proteoglycan aggregate complex of cartilage and chondroitin sulfate (shark cartilage 740 mg per capsule, twice daily)	at least one mucopolysaccharide compound in an amount which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent
about 50-100 mg lecithin; about 12.5-40 mg phosphatidyl choline; about 225 mg EPA from fish oil; and 500 mg flaxseed oil (equivalent of about 275-325 mg linolenic acid)	at least one polar surface active lipid
about 10.6 g twice daily of Neocate infant formula in the genetic code and molar ratio of human tissue, (breast milk and stem cell human tissue)	a plurality of amino acids, no more than 10% of which are in the D-form, in a molar ratio which is characteristic in healthy tissue of the type being treated for damage

8. Symptoms of severe abdominal pain and diarrhea, and flare-up in this Crohn's disease patient were cleared within 24 hours after treatment of the medicament described in paragraph 7. The improvement continued over the next few weeks, and the patient responded to the least amount of corticosteroids, which was alternating daily dosages of a half a tablet (2 mg) with a full tablet (4 mg) required to prevent flare-ups in the past several decades of management. Severe unsightly bruising and poor healing of lacerations and associated intolerance of sutures in the patient were also reduced.

9. It was well-known at the time the present application was filed that a reduction in inflammation and the clearing of symptoms in Crohn's disease, such as those detailed above for this patient, are indicative of tissue healing. See, for example, the attached passage from Pathology, Rubin E and Farber JL (eds.), J.B. Lipincott Co., Phila. PA, 1988, p. 68, which reads (emphasis added):

> Man is constantly subjected to injuries that may result in cell death and tissue destruction. Healing, a response to this injury, represents an attempt to maintain normal structure and function. Healing overlaps with the inflammatory process, ***and it is only for didactic purposes that the two are separated.***

10. Although components of the presently-claimed medicaments are believed to have, of themselves, anti-inflammatory activity, the tissue healing processes initiated by the claimed compositions were not solely due to a reduction in inflammation, but are also the result of anabolism. The claimed medicaments provide L-amino acids in a molar ratio which is characteristic in healthy tissue of the type being treated for damage. As stated in the present application, at pg. 13, lns. 5-8 and at pg. 13, ln. 17 to pg. 14, ln. 1:

> [I]t is believed that the inventive therapeutic formulations work to promote tissue repair by providing stem cells with the optimal ratios and proper stereoisomer form of amino acids that are needed to synthesize new tissue . . .
>
> [B]y altering the balance of free L amino acids such that under the law of mass action, protein synthesis is favored over proteolysis. By adding additional free amino acids, the activity of enzymes involved in protein synthesis and

degradation, such as proteases, is driven in the direction of protein synthesis and therefore in the direction of tissue production rather than protein degradation. Also, it is believed that the addition of L amino acids inhibits or arrests the catabolic protein degradation reactions of these enzymes.

Thus, the claimed medicaments promote tissue healing by reducing inflammation while a the same time stimulating anabolic processes. This is in contrast to the action of anti-inflammatory drugs like aspirin or corticosteroids, which inhibit inflammation *without* stimulating anabolic processes.

11. From the clinical results and observations during the treatment of this Crohn's disease patient described above, I have therefore concluded that the anabolic processes of tissue protein synthesis and cell membrane repair/replacement had occurred as a result of administering the medicament according to the present invention described above. I have therefore successfully treated a patient with Crohn's disease with a medicament according to claim 1 of my patent application.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-referenced patent application or any patent issued thereon.

8-3-04 Leonard S. Girsh M.D

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Pathology

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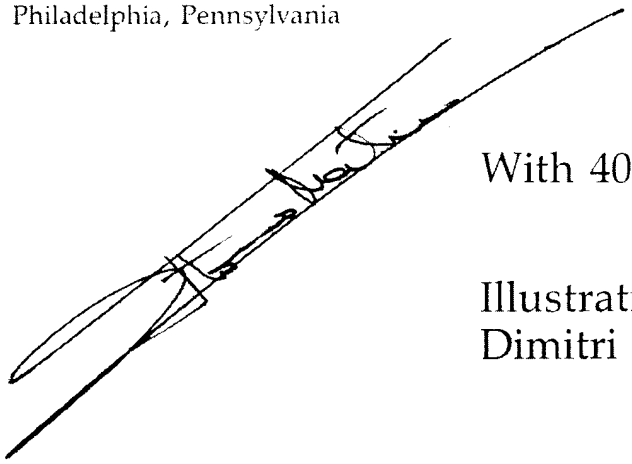

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and our wives:
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Man is constantly subjected to injuries that may result in cell death and tissue destruction. **Healing,** a response to this injury, represents an attempt to maintain normal structure and function. Healing overlaps with the inflammatory process, and it is only for didactic purposes that the two are separated. Some primitive organisms can replace almost any cell or tissue with a new one, a process called **regeneration.** Although regeneration is, in general, a desirable process, there are potential disadvantages. For example, replacement of neurons would require cell division, an event that could result in loss of all the information gathered and stored during the lifetime of the dividing cell. If every cell could be regenerated there would be no death. On the other hand, if lost cells could not be replaced, the life span of most organisms would be drastically curtailed. Organisms exist between these two ends of the spectrum, with the balance somewhat biased toward regeneration.

When the cell membrane of an amoeba is punctured, the immediately adjacent cytoplasm condenses, sealing the defect and producing a new cell membrane. This reaction may be viewed as a primitive healing reaction. In multicellular organisms, the healing process is more complex. Invertebrates and amphibians can replace lost parts: Lobsters regrow lost claws, salamanders develop a new lens from the iris, and newts replace lost extremities. The process of regenerating whole limbs is termed **axial regeneration.**

When a newt's limb is amputated, the epidermal cells adjacent to the wound divide and rapidly cover the stump. Epithelial cell proliferation continues and the cells pile up at the apex, forming an apical cap. The connective tissue cells in the stump—fibroblasts, myocytes, and osteocytes—divide. The daughter cells lack some of the differentiated properties of the parent cells, the result of a process called **dedifferentiation.** The dense extracellular matrix originally present in the stump is catabolized and replaced by a loose, edematous stroma resembling embryonic mesenchyme. The combination of mesenchymal cells embedded in a loose, edematous stroma is termed the **blastema.** The blastemal cells multiply rapidly, endothelial cells proliferate and vascularize the blastema, and orderly differentiation into bone, muscle, tendon, arterioles, capillaries, and venules follows. The end result is the accurate replacement of the lost part.

This complex mechanism of axial regeneration is presumably controlled by the genetic information contained in the cells of the stump; amputation triggers the expression of this information, which is repressed after embryonic development. However, not all the genetic information in the cells of the stump is expressed. The cells proximal to the amputation repress the formation of proximal structures, since only the distal structures are regenerated. **As we ascend in the phylogenetic scale from reptiles to birds and mammals, repression is favored over derepression.** In mammals, granulation tissue, which replaces lost tissue, is reminiscent of the amphibian blastema. However, rather than forming a limb, granulation tissue matures only into dense connective tissue and eventuates in a scar. This replacement of lost tissue by scar tissue is termed **repair.** There are two major components of the repair reaction, the extracellular matrix and the cells.

The Extracellular Matrix

The extracellular matrix is a stable complex of macromolecules that underlies epithelia and surrounds connective tissue cells. Although the glycosaminoglycans of a bacterium's capsule constitute a primitive extracellular matrix, a complex extracellular matrix resulting from the interaction of several macromolecules is the hallmark of multicellularity. An inert glue cannot distribute and maintain cells in a predetermined and yet dynamic pattern. Only a matrix that contains information can direct migration, attachment, differentiation, and organization of the cells. The importance of the extracellular matrix for multicellularity is indicated by the production of collagen, laminin, and fibronectin as early as cleavage of the fertilized ovum. The information contained in the extracellular matrix is important not only for development but also for wound healing.

In spite of the differences in tertiary structure, physical properties, and biologic context, the matrix proteins of invertebrates, fish, reptiles, birds, and mammals share a common plan. A third of their amino acid content is glycine, and they are rich in the amino acids serine, proline, threonine, and alanine. These four amino acids are coded by RNA triplets with cytosine and uracil as the second and third residue, and differ from each other only in the first residue of the code. Proteins with great apparent disparities—the invertebrate fibroin, silk, and resilin, for example, as well as human collagens and elastin—share this common plan. Although it is conceivable that this similarity could result from evolutionary convergence, it is more likely that the present polymorphism is the result of evolution from a single primordial gene.

The extracellular matrix not only provides tissues with structural support but also exchanges information with cells, thereby modulating a host of processes, including development, cell migration, at-